

**AMENDMENTS TO THE CLAIMS**

1. (Previously Presented) A non-human transgenic animal capable of producing heterologous T-cell receptors, comprising:  
inactivated endogenous T-cell receptor loci; and  
transgenes contained within its genome composed of un rearranged human T-cell receptor alpha and beta loci, wherein expression of the transgenes is controlled by human T-cell receptor loci regulatory sequences and wherein said animal is capable of productive rearrangement of the human T-cell receptor alpha and beta loci to encode functional heterologous T-cell receptors.
2. (Original) The non-human transgenic animal of claim 1, wherein said inactivated endogenous T-cell receptor loci are  $\alpha$  and  $\beta$  chain T-cell receptor loci.
3. (Cancelled)
4. (Previously presented) The non-human transgenic animal as in one of claims 1-2, wherein said human T-cell receptor loci are composed, in operable linkage, of a plurality of human T-cell receptor V genes, and D and /or J and C genes.
5. (Previously Presented) The non-human transgenic animal as in one of claims 1-2, wherein said animal is capable of productive VDJC rearrangement and is capable of expressing heterologous T-cell receptors.
6. (Previously presented) The non-human transgenic animal as in one of claims 1-2, wherein said transgenes undergo productive VDJC rearrangement in lymphocytes of said non-human transgenic animal and wherein T-cells express detectable amounts of transgenic TCR in response to antigenic stimulation.
7. (Previously presented) The non-human transgenic animal as in one of claims 1-2 wherein said non-human transgenic animal produces an immune response to an antigen, said immune response comprising a population of T-cells reactive to an antigen and wherein the T-cell receptors comprise a human T-cell receptor.
8. (Cancelled)

9-29 (Cancelled)

30. (Previously presented) The non-human transgenic animal as in one of claims 1-2, wherein said animal is any animal which can be manipulated transgenically.

31. (Previously presented) The non-human transgenic animal as in one of claims 1-2, wherein said animal is a mouse.

32 – 37 (Cancelled)

38. (Previously Presented) A method of producing a non-human transgenic animal capable of productive rearrangement of the human T-cell receptor  $\alpha$  and  $\beta$  loci and of producing heterologous T-cell receptors comprising the steps of:

inactivating endogenous T-cell receptor loci in an embryo or embryonic stem cell;

inserting transgenes containing active, unrearranged  $\alpha$  and  $\beta$  chain human T-cell receptor loci in said embryo or embryonic stem cell, wherein expression of the transgenes is controlled by T-cell receptor loci regulatory sequences;

producing a transgenic animal from said embryo or embryonic stem cell which contains the active human transgene wherein the animal is capable of producing T-cells that express functional heterologous human T-cell receptors; and

breeding the transgenic animal as needed to produce the transgenic animal and its progeny capable of producing heterologous T-cell receptors.

39. (Original) The method of claim 38 wherein said endogenous T-cell receptor loci are  $\alpha$  and  $\beta$  chain T-cell receptor loci.

40. (Cancelled)

41. (Previously Presented) A method of producing a non-human transgenic animal capable of productive rearrangement of the human T-cell receptor  $\alpha$  and  $\beta$  loci and of producing heterologous T-cell receptors comprising the steps of:

inactivating endogenous T-cell receptor loci in an embryo or embryonic stem cell, wherein said loci are T-cell receptor  $\alpha$  or T-cell receptor  $\beta$  loci;

producing a transgenic animal from said embryo or embryonic stem cell which contains inactivated loci wherein the animal is incapable of expressing said endogenous loci;

crossing a produced transgenic animal having inactivated endogenous T-cell receptor  $\alpha$  loci with a produced transgenic animal having inactivated endogenous T-cell receptor  $\beta$  loci;

selecting progeny having both inactivated endogenous T-cell receptor  $\alpha$  and T-cell receptor  $\beta$  loci;

inserting transgenes containing active, unrearranged human T-cell receptor loci in an embryo or embryonic stem cell wherein said human T-cell receptor loci are human T-cell receptor  $\alpha$  or T-cell receptor  $\beta$  loci, wherein expression of the transgenes is controlled by T-cell receptor loci regulatory sequences;

producing a transgenic animal from said embryo or embryonic stem cell which contains the active human transgene;

crossing a produced transgenic animal having active human T-cell receptor  $\alpha$  transgenes with produced transgenic animal having active human T-cell receptor  $\beta$ -transgenes;

selecting progeny having both active human T-cell receptor  $\alpha$  and T-cell receptor  $\beta$  transgenes wherein the animal is capable of producing T-cells that express functional heterologous human T-cell receptors;

crossing a produced transgenic animal having both inactivated endogenous T-cell receptor  $\alpha$  and T-cell receptor  $\beta$  loci with a produced transgenic animal having both active human T-cell receptor  $\alpha$  and T-cell receptor  $\beta$  transgenes;

selecting progeny having inactivated endogenous T-cell receptor  $\alpha$  and T-cell receptor  $\beta$  loci and containing active human T-cell receptor  $\alpha$  and T-cell receptor  $\beta$ -transgenes; and

breeding the transgenic animal as needed to produce the transgenic animal and its progeny capable of producing heterologous T-cell receptors.

42. (Previously presented) The method as in one of claims 38, 39, 41 wherein said endogenous T-cell receptor loci are inactivated by a functional limitation of the loci.

43. (Previously presented) The method as in one of claims 38, 39, 41 wherein said endogenous T-cell receptor loci are inactivated by deleting J segment genes from said loci.

44. (Previously presented) The method as in one of claims 38, 39, 41 wherein said endogenous T-cell receptor loci are inactivated by deleting D segment genes from said loci.

45. (Previously presented) The method as in one of claims 38, 39, 41 wherein said endogenous T-cell receptor loci are inactivated by deleting C segment genes from said loci.

46. (Cancelled)

47. (Previously Presented) The method as in one of claims 38, 39, 41 wherein said transgenes containing the active human T-cell receptor loci comprise, in operable linkage, a plurality of human T-cell receptor V genes, and D and/or J and C genes.

48 – 111. (Cancelled)

112. (Previously Presented) A non-human transgenic animal comprising inactivated endogenous T-cell receptor gene loci, said transgenic animal further containing in its genome transgenes composed of unrearranged human T-cell receptor  $\alpha$  and  $\beta$  loci, comprising, in operable linkage, a plurality of human T-cell receptor V genes, and their D and /or J and C genes, wherein said animal is capable of productive rearrangement of the human T-cell receptor alpha and beta loci to encode functional heterologous T-cell receptors.

113. (Previously Presented) A non-human transgenic animal having a germline genome with:

a human T-cell receptor  $\beta$  chain transgene comprising in operable linkage a plurality of human V genes, and either one or both of the C  $\beta$  loci and wherein in lymphocytes of said non-human transgenic animal the human T-cell receptor  $\beta$  chain transgene undergoes productive VDJ rearrangement and produces T-cells expressing TCR human  $\beta$  chain in detectable amounts in response to antigenic stimulation;

a human T-cell receptor  $\alpha$  chain transgene with plurality of human V gene segments, human J gene segments, the human C  $\alpha$  coding exon, and a human 3' downstream  $\alpha$ -enhancer; and wherein in lymphocytes of said non-human transgenic animal the human T-cell receptor  $\alpha$  chain transgene undergoes productive VJ rearrangement and produces T-cells expressing TCR

human  $\alpha$ -chain in detectable amounts in response to antigenic stimulation;  
an endogenous TCR  $\beta$  chain loci having an inactivated  $\beta$  chain gene; and  
an endogenous TCR  $\alpha$  chain loci having an inactivated  $\alpha$  chain gene.

114. (Currently Amended) The non-human transgenic animal of claim 1 or 2, wherein the human TCR  $\alpha$  locus contains all of the human TCR  $\alpha$  V region, J region and C region genes.

115. (Currently Amended) The non-human transgenic animal of claim 114, wherein the human TCR  $\beta$  locus contains all of the human TCR  $\beta$  V region, D region, J region and C region genes.

116. (Previously Presented) The non-human transgenic animal as in one of claims 1-2, wherein said animal is capable of producing a repertoire of functional heterologous TCRs.

117. (Previously Presented) The non-human transgenic animal of claim 5, wherein expression of the heterologous T-cell receptors is necessary for T-cell development, T-cell maturation or antigen stimulated responses.

118. (Previously Presented) The non-human transgenic animal of claim 5, wherein the heterologous T-cell receptors are expressed on pre-T cells so to effect T-cell development, produce mature, functional T-cells, or elicit an effective antigen-stimulated response.